REMARKS

In response to the Final Office Action dated January 22, 2008, and further to the Notice of Appeal filed on July 22, 2008, Applicants have amended claims 1-3. No claims have been canceled and no new claims have been added. It is urged that support for all the above amendments may be found throughout the specification as originally filed, for example, at page 18, lines 18-19. No new matter has been added. The above amendments are not to be construed as acquiescence with regard to the Examiner's rejections and are made without prejudice to prosecution of any subject matter removed or modified by this amendment in a related divisional, continuation or continuation-in-part application. Following the amendments, claims 1-6, 8, 10, 13, 15, 25-26, and 43 are pending in the application. Favorable reconsideration of the subject application is respectfully requested in view of the above amendments and the following remarks.

Rejections under 35 U.S.C. §112, first paragraph, written description

Claim 1-6, 8, 10, 13, 15, 25-26, and 43 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to satisfy the written description requirement. Specifically, the Examiner asserts that the genus of claimed nucleic acid molecules encoding a sphingosine kinase functional fragment, or homologue thereof lacks sufficient recitation of distinguishing identifying characteristics and that the specification does not provide written description support for the claimed genus. Further, the Examiner alleges that the claim does not require that the produced protein possess any particular biological activity, conserved structure, or other distinguishing feature, and thus, is drawn to a genus of nucleic acids that is defined only by sequence identity. Therefore, the Examiner concludes that the claimed subject matter was not described in such a way as to convey to the skilled artisan that the inventor was in possession of the claimed invention at the time of filing of the instant application.

Applicants respectfully traverse this basis of rejection and submit that the as-filed specification adequately provides written description support for the presently claimed nucleic acids encoding sphingosine kinase, functional fragments thereof or homologs thereof. Applicants, without acquiescence, have amended claims 1-3 to recite on isolated nucleic acid molecule encoding sphingosine kinase or functional fragment or homolog thereof that comprises

sphingosine kinase activity. Support for the amendment can be found throughout the specification as filed, for example, on page 18, lines 18-19.

The Examiner contends that the presently claimed nucleic acids are only defined by sequence identity. In contrast, the Examiner concludes that the presently claimed nucleic acids lack sufficient identifying characteristics. Applicants are confused as to how the presently claimed nucleic acids, which are defined by sequence identity (*i.e.*, a structural characteristic), lack sufficient identifying characteristics. Applicants respectfully disagree with the Examiner and submit that the as-filed specification provides sufficient identifying characteristics to describe the presently claimed isolated nucleic acid molecules encoding sphingosine kinase or functional fragment or homolog thereof.

The Examiner further contends that genes coding for a sphingosine kinase functional fragment or homolog thereof, have not been disclosed and that there is no evidence of record where the specification teaches any characteristics of a sphingosine kinase functional fragment or homolog thereof that would distinguish it from a non-natural variant constructed by the hand or man. Applicants are confused by the Examiner's rationale and request clarification. Applicants respectfully submit that the present claims are drawn to isolated nucleic acids, *i.e.*, those made by the hand of man.

The Examiner further contends that the claims are "extremely broad since insufficient guidance is provided as to which of the plethora of fragments of nucleic acids encode sphingosine kinase polypeptides which will retain the characteristics of a functional sphingosine kinase." Applicants respectfully submit that the mouse, rat, monkey, *S. cerevisiae*, *S. pombe*, *A. thaliana*, and *O. sativa* sphingosine kinase DNA and protein sequences were known prior to the effective filing date of the instant application (Pitson et al., 2002 and Kohama et al., 1998, previously made of record). Furthermore, the foregoing references identified at least five regions with an extremely high degree of sequence conservation, including the nucleotide binding site and several post-translational phosphorylation motifs (see Kohoma et al., 1998, e.g., kinase A, casein kinase II, and protein kinase C) in species from human to rice (see Figure 1, Pitson et al. 2002; Kohama et al., 1998; and Pitson et al., *Biochem J.* Sep 1;350 Pt 2:pp. 429-41,2000).

Applicants respectfully submit that not only were numerous homologs known in the art, but, in addition, all the homologs identified possess an extremely high degree of sequence

identity in the nucleotide binding domain (see abstract, Pitson et al., 2002), which is required for sphingosine kinase activity.

Moreover, Pitson et al. describe deletions, trucations, and point mutants in these conserved regions in the human sphingosine kinase in order to identify the active site of the enzyme (*e.g.*, $SGDGX_{17\text{-}21}K$ in Figures 1-3 and Table 1 of Pitson et al., 2002). Thus, in direct contrast to the reasoning supplied by the Examiner, the skilled artisan would appreciate important conserved sequences, functional fragments and homologs of sphingosine kinase as evidenced by Pitson et al., 2002 and Kohama et al., 1998. Moreover, the skilled artisan would appreciate how to assay for sphingosine kinase activity as such assays were well known in the art at the time of filing the instant application, and are in fact made explicit reference to in Example 1 of the as-filed specification (p. 47, lines 16-22, referencing Xia et al., *P.N.A.S.* Vol. 95, pp. 14196-14201, 1998).

Applicants respectfully submit that the skilled artisan would recognize the presently claimed isolated nucleic acid molecules were in possession of Applicants at the time of filing the instant specification. Moreover, nucleic acids encoding sphingosine kinase or functional fragment or homolog thereof, wherein said kinase, functional fragment thereof, or homolog thereof comprising sphingosine kinase activity were known in the art at the time of filing the instant specification.

Accordingly, reconsideration and withdrawal of this basis for rejection is respectfully requested.

Rejections under 35 U.S.C. §112, first paragraph, enablement

Claims 1-6, 8, 10, 13, 15, 25-26, and 43 stand rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for overexpression of a nucleic acid encoding sphingosine kinase introduced into mammalian endothelial cells that results in enhancing cell survival, altering adhesion molecule expression, enhancing neutrophil adhesion to endothelial cells, promoting tube formation or formation of a capillary network of endothelial cells *in vitro*; the specification allegedly does not reasonably enable the modulation one or more mammalian endothelial cell functional characteristics by way of the claimed methods *in vivo*. Specifically, the Examiner contends that the specification fails to provide any relevant teachings

or specific guidance or working examples with regard to the production of sphingosine kinase *in vivo*, by modulating the functional level of sphingosine kinase in a mammal resulting in the treatment and/or prophylaxis of a condition characterized by aberrant or otherwise unwanted endothelial cell function. Therefore, the Examiner concludes that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate with the scope with the claims.

Applicants respectfully traverse this basis of rejection and submit that the presently claimed invention is fully enabled by the as-filed specification. Moreover, Applicants respectfully submit that the skilled artisan would not encounter any undue experimentation in practicing the full scope of the presently claimed invention.

The Examiner contends that *in vitro* examples do not reasonably provide guidance for the *in vivo* delivery of a nucleic acid molecule encoding a sphingosine kinase or functional fragment or homolog thereof such that the endothelial cell functional characteristics are modulated. Applicants respectfully disagree and submit that the as-filed specification provides ample guidance to accomplish overexpression of an isolated nucleic acid molecule encoding sphingosine kinase *in vitro* and *in vivo* to modulate endothelial functional cell characteristics, or functional fragment or homolog thereof, wherein said kinase, functional fragment thereof, or homolog thereof comprises sphingosine kinase activity. Applicants reiterate that the use of *in vitro* experiments to establish *in vivo* events is, in principle, a valid methodology. Cross v. Iizuka, 753 F.2d 1040, 1050, 224 U.S.P.Q. 739 (Fed. Cir. 1985); Nelson v. Bowler, 626 F.2d 853, 856, 206 U.S.P.Q. 881 (C.C.P.A. 1980).

Applicants respectfully submit that the as-filed specification teaches that overexpression of sphingosine kinase using an adenoviral vector *in vitro* leads to increased endothelial cell survival in adenoviral treated cells compared to control cells (see Example 1 of the as-filed specification). Furthermore, endothelial cells treated *in vitro* with adenoviral sphingosine kinase display lower levels of caspase-3 activity compared to control cells (see Example 1 of the as-filed specification). Example 2 of the as-filed specification shows that endothelial cells treated *in vitro* with adenoviral sphingosine kinase display increased vascular cell adhesion molecule expression, increased neutrophil adhesion, and vascular tube formation.

The Examiner contends that the delivery of a nucleic acid to tissue culture cells does not provide guidance for overcoming the obstacles of *in vivo* delivery, because the nucleic acid does not have to cross through the complex organization of organs and tissues. Further, the Examiner contends that cell cultures do not mimic *in vivo* organs in that there is no three dimensional structure, blood vessels, or connective tissue through which the nucleic acid would be required to cross through *in vivo*. Applicants respectfully submit that one having ordinary skill in the art would readily appreciate that adenoviral gene delivery is targeted (*e.g.*, direct infection, direct injection, etc.) in order to delivery a particular therapy. Applicants submit that the skill in the art of adenoviral administration is high and that one having skill in the art would not encounter undue experimentation in delivering an adenovirus to a given treatment site. Complex experimentation is not undue, and further, such experimentation is routine in the art of gene therapy as the Examiner pointed out in the Office Action issued May 3, 2007 (see Gnuwuch et al., 2002).

Furthermore, Applicants reiterate that the presently claimed method need not require the injection of adenovirus into the mammal, but rather, may comprise *in vitro* modification of the desired cells with adenoviral sphingosine kinase and subsequent transfer of said cells into said mammal in order to exert a therapeutic effect (see p.34, lines 7-15, and claim 15).

The Examiner further contends that *in vitro* studies of a protein's function at the cellular level is problematic due to interactions with other molecules and precludes the studies of physiological (*e.g.*, metabolic pathways) and phenotypic functions in a mammal (*e.g.*, role of the protein in the whole mammal). Applicants fail to understand the Examiner's rationale. Such rationale would preclude the correlation of any in vitro assay to an in vivo assay, unless the assay environments were indistinguishable. Applicants respectfully submit that this rationale is not only impractical, but irrelevant. The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers,* 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), aff 'd. subnom., *Massachusetts Institute of Technology v. A.B. Fortia,* 774 F.2d 1104, 227 USPQ 428 (Fed. Cir.1985). See also *In re Wands,* 858 F.2d at 737, 8 USPQ2d at 1404. The test of

enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976).

Applicants further submit that Duan et al., 2007, previously made of record, provides post-filing examples of the reduction to practice of adenoviral sphingosine kinase administration in mammals. In addition, the reference correlates *in vitro* observations to support their studies. In fact, Duan et al. expressed sphingosine adenovirus in isolated rat cardiac myocytes, isolated rat hearts, and *in vivo* rat hearts. In each case, the adenoviral sphingosine kinase was overexpressed (see, for example, Figures 1, 2, and 7 of Duan et al.) Furthermore, adenoviral sphingosine kinase expression in isolated rat hearts having an ischemic injury led to decreased creatine kinase expression (released during cardiac myocyte cell death) and improved the hemodynamics following reperfusion. Thus, in this aspect, *in vitro* cell survival of cardiac myocytes expressing sphingosine kinase adenovirus would correlate with the decrease in creatine kinase expression in isolated rat hearts expressing sphingosine kinase adenovirus (i.e., both effects are due, in part, to decreased cell death). Duan et al. also show that *in vivo* administration of a sphingosine kinase adenovirus to rat hearts comprising an ischemic injury increased neovascularization and improved the morphology in sphingosine kinase treated heart compared to control hearts (see, for example, Figures 7 and 8 of Duan et al.). Furthermore, Duan et al. specifically state that "[b]ecause SPK1 protects a variety of cells, including cardiac myocytes, against apoptosis induced by different stimuli, it is reasonable to predict that the protective effects of SPK1 on the heart come, at least in part, from the suppression of cell death induced by ischemia/reperfusion injury *in vivo* (see page 8, 2nd column, 1st full paragraph). As set forth by the Supreme Court and stated by the Federal Circuit, "[t]he test of enablement is whether one of ordinary skill in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." *United States v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988).

The Examiner further contends that the instant specification does not provide any relevant teachings, specific guidance, or working examples for overcoming the limitations of sphingosine kinase gene transfer *in vivo* resulting in the modulation of endothelial cells *in vivo* in the treatment and/or prophylaxis of a disease raised by the state of the art. Applicants

respectfully submit that a clinical reduction to practice is not a prerequisite to enable a method for treating a mammal *in vivo*. Applicants have conclusively shown that over-expression of sphingosine kinase in an adenoviral vector modulates the characteristics of endothelial cells as claimed, and thus, provides sufficient enablement for the skilled artisan to accomplish the presently claimed methods *in vivo*.

Furthermore, Applicant submits that enablement of the claimed invention does not require a demonstration that the invention may be used therapeutically. Applicant submits that the Federal Circuit has clearly established that human clinical data sufficient to gain FDA approval is not required to establish patentability. In the landmark case of *In re Brana*, the Federal Circuit held that the FDA's requirements of testing for safety and effectiveness are not required by the patent laws. The Court stated, "[t]he Commissioner, as did the Board, confuses the requirement under the law for obtaining a patent with the requirements of obtaining government approval to market a particular drug for human consumption." 51 F.3d 1560, 1567 (Fed. Cir. 1995). The Court continued by stating that "[u]sefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans." *Id.* at 1568. Applicant also notes that the rejection described in *In re Brana* was made under Section 112 and not under Section 101.

The Examiner's assertions, in part, appear to be that the specification does not enable the use of the claimed methods due to a lack of evidence regarding their *in vivo* human implementation. If this is true, the Action is asserting that the claimed invention lacks *in vivo* utility. Although this rejection is not made under 35 U.S.C. § 101, the legal standard to be applied is the same. *In re Brana*, 51 F.3d 1560 (Fed. Cir. 1995) (Although the Examiner rejected pharmaceutical compositions based on § 112, a § 101 rejection for lack of utility would also have been proper.) (See also "Legal Analysis Supporting Utility Examination Guidelines 60 F.R. 36263, July 14, 1995.)

Applicant respectfully submits that this rejection is improper in view of the PTO Guidelines. In *no* case has a Federal court required an applicant to support an asserted utility with data from human clinical trials. Moreover, in *In re Brana*, the Federal Circuit emphatically

rejected the PTO position that human clinical testing is necessary to establish practical utility for an antitumor agent. 51 F.3d 1560. Importantly, the court noted, citing *In re Krimmel*, 130 U.S.P.Q. 205 (C.C.P.A. 1961):

> We hold as we do because it is our firm conviction that one who has taught the public that a compound exhibits some desirable pharmaceutical property in a standard experimental animal has made a significant and useful contribution to the art, **even though it may eventually appear that the compound is without value in the treatment of humans**. (Emphasis added)

Here, the situation is analogous. The Applicant has demonstrated a method of directing an effector molecule linked to an interactive molecule to an apoptotic cell in a neoplastic environment; whether the method will eventually have commercial value in the treatment of humans is not a relevant inquiry to determine patentability.

Applicant submits that in view of the as-filed disclosure, one having ordinary skill in the art would not encounter any undue experimentation in practicing the entire breadth of the presently claimed invention. Accordingly, Applicant submits the as-filed specification fully enables the presently claimed invention. Reconsideration and withdrawal of this basis for rejection is respectfully requested.

Double patenting rejections

Claims 1-3, and 5 stand rejected for non-statutory obviousness-type double patenting as allegedly being unpatentable over claims 1-6, 15-20 of U.S. Patent No. 10/275,686.

Further, claims 1-2, 5-7, and 15 stand rejected for non-statutory obviousness type double patenting as allegedly being unpatentable over claims 1-15, 17, and 23 of U.S. Patent No. 09/977,217.

Applicants respectfully traverse this rejection and submit that the pending claims have not issued and the Examiner has not indicated that they are allowable, and thus, the present claims may be considerably amended during prosecution. As the 10/275,686 and 09/977,217 are presently owned by the same entity of the present application, Applicants request that this rejection be withdrawn in this application with the understanding that Applicants will file a Terminal Disclaimer, if appropriate, in the instant application. Until such time as the present

claims are in condition for allowance, Applicants respectfully submit that the filing of a terminal disclaimer is premature.

The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

All of the claims remaining in the application are now believed to be allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

Respectfully submitted,

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